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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,871	04/11/2005	Hans-Georg Kreysch	MERCK-2990	4478

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,871	KREYSCH ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 30-40 are pending and are being acted upon in this Office Action.

2. Copy of the following reference not previously applied is enclosed:

3. Stryer et al, in Biochemistry, Third edition, W H Freeman Company, New York, pages 31-33, 1998.

4. A notice of cited reference form PTO-892 is also enclosed.

5. In view of the amendment filed 12/3/08, the following rejection remains.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 30 and 33-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any second antibody or portion thereof that binds to any second epitope on the ErbB1 receptor wherein the second epitope located on the ErbB1 receptor molecule are located within the ErbB1 receptor ligand-binding domain.

Newly added claims 30 and 33-40 encompasses a pharmaceutical composition comprising a first antibody is murine, chimeric or humanized MAb 425 or murine, chimeric or humanized MAb225 or portion thereof that binds to a first epitope on the ErbB1 receptor and any second antibody or portion thereof that binds to a second epitope on the ErbB1 receptor wherein the second epitope located on the ErbB1 receptor molecule are located within the ErbB1 receptor ligand-binding domain.

The specification discloses only a pharmaceutical composition comprising a combination of two antibodies or a binding fragment thereof that binds to different epitopes on the extracellular domain of ErbB1 receptor to which the ligand binds. These anti-EGFR (ErbB1) antibodies are murine MAb 425, humanized antibody (h425) thereof, chimeric antibody (c425) thereof or a binding fragment thereof, such as a $F(ab')_2$, and murine MAb 225, humanized antibody (h225) thereof, chimeric antibody (c225) thereof or a binding fragment thereof such as a $F(ab')_2$. Most preferred is the combinatorial application of humanized MAb 425 and chimeric MAb 225 as a whole antibody or as $F(ab')_2$ fragment for a pharmaceutical composition, see page 6, lines 20-25. The pharmaceutical composition mentioned above further comprises a cytotoxic drug, cytokine, or a chemotherapeutic agent.

With the exception of the combination of the specific first and second antibodies mentioned above, there is insufficient written description about the binding specificity associated with the structure (the six CDRs 1-3 of immunoglobulin heavy and light chains) of any second antibodies or binding portion thereof that bind to any epitope located within the ErbB1 receptor ligand-binding domain for the claimed pharmaceutical composition or kit, in turn, useful for treating all types of cancer.

The specification discloses only a specific pharmaceutical composition comprising a specific combination of MAb 425, or humanized (h425) or chimeric (c425) or a binding fragment thereof and a monoclonal MAb 225, humanized (h225), chimeric (c225) or binding fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of second antibodies to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following are new ground of rejections.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 30-31, 33, 35-37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No. 4,943,533 (of record, issued July 24, 1990; PTO 892), Fan et al (newly cited, Cancer Research 53: 4322-4328, 1993; PTO 892), Ciardiello et al (newly cited Clinical Cancer Research 5: 909-916, April 1999; PTO 892), and Gill et al (newly cited, J Biol Chemistry 259(12): 7755-7760, 1984; PTO 892).

The '157 patent teaches a pharmaceutical composition comprising at least one antibodies specific for epidermal growth factor receptor (also known as ErbB1) such as MAb 425 and at least one antibody that binds to p185c-neu (also known as ErbB2 or HER2 or EGFR2) for treating tumor (see claim 4 of the '157 patent). The reference term "at least one" implies the reference composition comprising one or more antibodies of the same ErbB1 receptor type. The term "comprising" is open-ended. It expands the claimed pharmaceutical composition to include additional antibodies such as one or more antibodies that bind to p185c-neu as taught by the '157 patent. The '157 patent teaches an antibody that binds to the extracellular domain of human EGFR such as a monoclonal antibody MAb425 and it inhibits EGF binding to its receptor and induces EGF receptor down-regulation without stimulating EGF receptor tyrosine kinase activity (see claim 4 of the '157 patent, col. 12, line 7-11, in particular). The '157 patent teaches another monoclonal antibody that binds to EGFR such as M294 from ICN biomedicals (see col. 7, lines 38-40, in particular). The '157 patent teaches monoclonal antibodies that bind to the extracellular domains may be selected by screening for binding to the extracellular domains of EGFR (see col. 4, lines 64-67 bridging col. 5, lines 1-7, col. 2, lines 37-42, in particular). The reference EGFR extracellular domains to which the reference antibodies bind are located within the EGF ligand

binding domains because the reference antibodies such as MAb425, chimeric antibodies (see col. 5, lines 40-52, and binding fragment thereof (see col. 5, line 60-63, in particular) bind to the extracellular cellular domains of EGFR (see col. 12, lines 7-11, in particular). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical antibody MAb 425 and chimeric MAb 425, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

The invention in claim 30 differs from the teachings of the reference only in that the pharmaceutical composition wherein first antibody is murine monoclonal antibody MAb425 or chimeric MAb 425 and a second antibody or binding fragment thereof that binds to different epitopes located on the an ErbB1 receptor (EGFR) to an epitope different from the first antibody.

The invention in claim 31 differs from the teachings of the reference only in that the pharmaceutical composition wherein first antibody is murine monoclonal antibody MAb425 or chimeric MAb 425 and the second antibody is murine or chimeric MAb 225.

The '533 patent teaches various monoclonal antibodies such as MAb 225, 579 and MAb 455 that bind to human epidermal growth factor receptor (ErbB 1) and competes with the ligand for binding to the EGRF receptor (see entire document, col. 3, line 46-53, col. 8 through 10, in particular). The reference murine monoclonal antibody 225 inhibits the growth of A-431 tumor cells in the absence of ligand (see col. 8, lines 15, in particular) while the reference murine monoclonal antibody 528 competes with the ligand EGF for binding to the EGFR *in vivo* (see col. 3, lines 46-55, col. 6, lines 39-42, in particular) and inhibits EGF stimulated protein kinase activity (signaling pathway) in A-431 tumor cells (see col. 7, lines 45-54, in particular). The '533 patent teaches that monoclonal antibody 225 binds to a single class of receptor sites on all three cell types by blocking the binding of EGF to EGFR on A-431 cells (see col. 8, lines 59-68, in particular); the C225 antibody, which is a chimeric human antibody, inhibits the proliferation of tumor cells in concentration dependent manner (see col. 9, lines 9-10, in particular). The '533 patent teaches monoclonal antibodies that bind to different epitopes on epidermal growth factor receptor may be of considerable therapeutic use and diagnostic uses (see abstract, col. 1, lines 60-68, in particular).

Fan et al teach various monoclonal antibodies such as Mab225 and Mab528, and binding fragment thereof such as Fab and $F(ab')_2$ which bind to EGFR and inhibit binding of EGFR to its

natural ligand EGF thereby preventing ligand-induced activation of EGFR tyrosine phosphorylation, and inhibit proliferation of cells expressing EGFR breast cancer cells (p. 4322, col. 2). Fan et al teach attempting to block the function of receptors for growth factors as an approach to cancer therapy and that they are using anti-EGFR antibodies, such as monoclonal antibody Mab225, as a pharmaceutical in a clinical setting for therapy of patients with malignancies expressing high levels of EGFR (p. 4322, col. 2). Fan et al teach that the F(ab')2 fragment of Mab225 could inhibit ligand binding and signaling of ligands to EGFR, however, it could not inhibit cell proliferation as effectively as bivalent Mab225, had reduced binding affinity to EGFR, and a shorter half-life. Fan et al conclude that EGFR blockade may be useful in antitumor therapy and that the demonstration of *in vivo* activity of bivalent Mab225 F(ab')2 fragment establishes that Mab225 can act as a pharmacological EGFR blocking agent. Fan et al suggests using a murine/human chimeric antibody for therapy in future trials (abstract; p. 4327, cols. 1-2).

Ciardiello et al teach various monoclonal antibodies such as MAb 225 and MAb 528 are two mouse monoclonal antibodies that bind to EGFR and compete with ligand for the receptor binding and block ligand-induced activation of EGFR tyrosine kinase. Ciardiello et al further teach chimeric human-mouse MAb 225 (MAb C225) which contains the human IgG1 constant (see page 910, col. 1, in particular). Giardiello et al teach the combination of MAb C225 and cytotoxic agent such as topotecan has cooperative anti-proliferative activity in treating cancer by induction of cell death (see page 911, col. 2, last paragraph, page 913, col. 1, in particular) or chemotherapeutic agent such as cisplatin (see page 914, in particular).

Gill et al teach various such as MAb 225, MAb 528 and 579 that are inhibitors of EGF binding to cell surface receptor expressed on A431 cells (see page 7756, page 7758, in particular). These antibodies compete with EGF for binding to EGFR and appears to be a mixed competitive and non-competitive inhibition, see page 7758, col. 1, in particular). Gill et al further teach in vivo 528 IgG blocked self-phosphorylation of the EGF receptor without detectable agonist activity (see page 7758, col. 2, in particular) and these antibodies are effectively reduce large number of active EGFR present on A431 cells (see page 7758, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute at one or more antibodies that bind to p185c-neu (EGFR2) in the pharmaceutical composition for treating tumor of the '157 patent for one or more of monoclonal

antibody such as MAb 225, 579 and MAb 455 as taught by the '533 patent that bind within the ErbB1 receptor ligand-binding domain as taught by Gill et al, Ciardiello et al and/or Fan et al to form a pharmaceutical composition comprising MAb 425 or chimeric MAb 425 and Mab225, C225 or Mab528. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the various monoclonal antibodies and chimeric antibody C225 that are useful for treating cancer as taught by Fan et al with other chemotherapeutic agent or

One having ordinary skill in the art would have been motivated with the expectation of success to substitute because the '533 patent teaches monoclonal antibodies that bind to different epitopes on epidermal growth factor receptor may be of considerable therapeutic use (see abstract, col. 1, lines 60-68, in particular) and the chimeric C225 antibody inhibits the proliferation of tumor cells in concentration dependent manner (see col. 9, lines 9-10, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to combine one or more antibodies that bind to different epitope located within the ErbB1 receptor ligand-binding domain because Fan et al teach various monoclonal antibodies such as Mab225 and Mab528, and binding fragment thereof such as Fab and $F(ab')_2$ which bind to EGFR and inhibit binding of EGFR to its natural ligand EGF thereby preventing ligand-induced activation of EGFR tyrosine phosphorylation, and inhibit proliferation of cells expressing EGFR breast cancer cells (p. 4322, col. 2). The Mab 225 and binding fragment thereof is useful for treating cancer (see page 4322, col. 2, in particular).

One having ordinary skill in the art would have been motivated with the expectation of success to combine one or more antibodies that bind to different epitope located within the ErbB1 receptor ligand-binding domain and chemotherapeutic agent or cytotoxic agent because Giardiello et al teach the combination of MAb C225 and cytotoxic agent or chemotherapeutic agents has cooperative antiproliferative active in treating cancer by induction of cell death (see page 911, col. 2, last paragraph, page 913, col. 1, in particular).

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose….[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). From the combined teachings of the references, it is apparent that one

of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

12. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,558,864 (of record, issued Sept 24, 1996; PTO 892) in view of Ye et al (of record, Oncogene 18: 731-738, 1999; PTO 892) and Ciardiello et al (newly cited, Clinical Cancer Research 5: 909-916, April 1999; PTO 892).

The '864 patent teaches humanized monoclonal antibody such as h 425 that binds to EGF receptor derived from murine monoclonal antibody MAb 425 (see entire document, claims of the '864 patent, in particular). The '864 patent teaches the advantages of humanized antibody h425 is that the humanized is less likely than either mouse 425 antibodies to raise an immune response in humans and more efficacious when used therapeutically in humans than either the mouse or chimeric 425 antibodies since the humanized antibody has a longer half-life in humans and the least likely to arise adverse immune response in human patient with tumor (see col. 22, lines 1-15, in particular). The reference h 425 is identical to the claimed humanized MAb (h425).

The invention in claim 32 differs from the teachings of the reference only in that the pharmaceutical composition further comprises a second antibody wherein the second antibody is chimeric MAb 225(c225) that binds to a different epitope located within the ErbB1 receptor ligand-binding domain.

Ye et al teach C225 is a human-mouse chimeric anti-EGF receptor MAb derived from MAb 225; this chimeric MAb 225 fully retains the activity of murine in competing with EGF for receptor binding and produces a similar or even improved spectrum of anti-tumor activities on a variety of xenograft human cancer (see page 731, col. 2 last paragraph, in particular).

Ciardiello et al teach various monoclonal antibodies such as MAb 225 and MAb 528 are two mouse monoclonal antibodies that bind to EGFR and compete with ligand for the receptor binding and block ligand-induced activation of EGFR tyrosine kinase. Ciardiello et al further teach chimeric human-mouse MAb 225 (MAb C225) which contains the human IgG1 constant (see page 910, col. 1, in particular). Giardiello et al teach the combination of MAb C225 and cytotoxic agent such as topotecan has cooperative anti-proliferative activity in treating cancer by induction of cell death (see page 911, col. 2, last paragraph, page 913, col. 1, in particular) or chemotherapeutic agent such as cisplatin (see page 914, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the humanized antibody h425 of the '864 patent with the chimeric antibody C225 as taught by Ye et al or Ciardiello et al to form a third pharmaceutical composition for the same purpose. In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose….[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

One having ordinary skill in the art would have been motivated with the expectation of success to combine the humanized antibody of the h425 of the '864 patent with the chimeric antibody C225 because Ye et al teach this chimeric MAb 225 fully retains the activity of murine in competing with EGF for receptor binding and produces a similar or even improved spectrum of anti-tumor activities on a variety of xenograft human cancer (see page 731, col. 2 last paragraph, in particular). One having ordinary skill in the art would have been motivated with the expectation of success to combine one or more antibodies that bind to different epitope located within the ErbB1 receptor ligand-binding domain and chemotherapeutic agent or cytotoxic agent because Giardiello et al teach MAb C225 is useful for treating cancer and the combination of cytotoxic agent or chemotherapeutic agents has cooperative antiproliferative active in treating cancer by induction of cell death (see page 911, col. 2, last paragraph, page 913, col. 1, in particular). The '864 patent teaches the advantages of using humanized antibody h425 is that the humanized is less likely than either mouse 425 antibodies to raise an immune response in humans and more efficacious when used therapeutically in humans than either the mouse or chimeric 425 antibodies since the humanized antibody has a longer half-life in humans and the least likely to arise adverse immune response in human patient with tumor (see col. 22, lines 1-15, in particular).

13. Claims 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No. 4,943,533 (of record, issued July 24, 1990; PTO 892), Fan et al (newly cited, Cancer Research 53: 4322-4328, 1993; PTO 892), Ciardiello et al (newly cited, Clinical Cancer Research 5: 909-916, April 1999; PTO 892), and Gill et al (newly cited, J Biol Chemistry 259(12): 7755-7760, 1984; PTO 892) as applied to

claims 30-31, 33, 35-37 and 40 and further in view of US Pat No. 5,861,449 (of record, issued Jan 1999; PTO 892).

The combined teachings of the '157 patent, the '533 patent, Fan et al, Ciardiello et al, and Gill et al have been discussed supra.

The invention in claim 37 differs from the combined teachings of the references only in that the pharmaceutical composition further comprising a chemotherapeutic agent wherein the chemotherapeutic agent is doxorubicin.

The invention in claim 38 differs from the combined teachings of the references only in that the pharmaceutical composition further comprising a cytotoxic agent wherein the cytotoxic agent is an ErbB receptor inhibitor, a VEGF receptor inhibitor, an anti-angiogenic agent or a cytokine.

The '449 patent teaches a pharmaceutical composition comprising one or more VEGF receptor inhibitor such as DC101 monoclonal antibody, or chimeric antibody thereof that binds to the extracellular domain of VEGF receptor such as Flt-1 (see entire document, col. 8, lines 1-50, col. 7, lines 4-5, in particular) alone or in combination with a cytotoxic agent or chemotherapeutic agent such as doxorubicin, taxol (see col. 7, lines 4-11, in particular) or a cytokine such as CSF (see col. 19, lines 34-35, in particular). The reference pharmaceutical composition comprises the reference antibody and the anti-neoplastic drug or chemotherapeutic drug as separate molecules (see col. 7, lines 9-11, in particular) to provide even more efficient treatment of inhibiting the growth of tumor cells than the use of the antibody by itself (see col. 7, lines 4-9, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the pharmaceutical composition comprising monoclonal Mab 425, or chimeric antibody thereof and MAb 225 as taught by the '157 patent, the '533 patent, Fan et al, Ciardiello et al, and Gill et al with the various cytotoxic agent or chemotherapeutic agent such as cisplatin, doxorubicin, taxol, VEGF receptor inhibitor such as DC101 or cytokine such as CSF as taught by the '449 patent for a pharmaceutical composition useful for treating cancer. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do so because the '449 patent teaches the combination provides even more efficient treatment by inhibiting the growth of tumor cells than the use of the antibody by itself (see col. 7,

lines 4-9, in particular). The '157 patent teaches antibody that binds to EGFR such as monoclonal antibody MAb425, chimeric antibody or binding fragment thereof that binds to the extracellular domain of human EGF receptor is useful for treating cancer. One having ordinary skill in the art would have been motivated with the expectation of success to combine one or more antibodies that bind to different epitope located within the ErbB1 receptor ligand-binding domain with chemotherapeutic agent or cytotoxic agent because Giardiello et al teach the combination of MAb C225 and cytotoxic agent or chemotherapeutic agents has cooperative anti-proliferative activity in treating cancer by induction of cell death (see page 911, col. 2, last paragraph, page 913, col. 1, in particular).

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose….[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

14. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No. 4,943,533 (of record, issued July 24, 1990; PTO 892), Fan et al (newly cited, Cancer Research 53: 4322-4328, 1993; PTO 892), Ciardiello et al (newly cited, Clinical Cancer Research 5: 909-916, April 1999; PTO 892), and Gill et al (newly cited, J Biol Chemistry 259(12): 7755-7760, 1984; PTO 892) as applied to claims 30-31, 33, 35-37 and 40 and further in view of US Pat No 6,342,219 (of record, filed April 28, 2000; PTO 892).

The teachings of the '157 patent, the '533 patent, Fan et al, Ciardiello et al, and Gill et al have been discussed supra.

The invention in claim 39 differs from the teachings of the combined references only in that a kit comprising the pharmaceutical composition of claim 30 in one package and a carrier in a second package.

The '219 patent teaches a pharmaceutical kit comprising distinct containers for each desired agent where combined therapeutics are provide (see col. 102, lines 5-31, in particular).

The '219 patent teaches such kit contains all the necessary reagents and means for commercial sale for treating cancer (see col. 102, lines 52-63, in particular). The kit may contain antibody and other reagent separately (see col. 102, lines 12-25, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to put the pharmaceutical composition comprising a first murine monoclonal antibody MAb425 or chimeric MAb 425 and a second antibody C225 or binding fragment thereof that bind to different epitopes located on the an ErbB1 receptor (EGFR) ligand binding domain of the '157 patent, the '533 patent, Fan et al, Ciardiello et al, and Gill et al in a first package and a separate package for any reagent as desired as taught by the '219 patent.

One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '219 patent (See column 102, lines 41-61, in particular). It is within the purview of one of ordinary skill in the pharmaceutical art to put any carrier in a separate package for stability and convenience of the practitioner as taught by the '219 patent (see col. 102, lines 12-25, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
February 29, 2008